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Results of computer-assisted sensory evaluation in 41 patients with erythromelalgia

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Summary

Background. Erythromelalgia is a rare disorder characterized by the clinical syndrome of burning pain, warmth and redness of the limbs. Neurological abnormalities (both large- and small-fibre neuropathy) are common. There have been few published reports on the sensory status of patients with erythromelalgia.

Aim. To investigate the results of quantitative sensation testing in erythromelalgia using computer-assisted sensory evaluation, including vibratory detection threshold, cool detection threshold and heat–pain threshold (HPT).

Methods. Patients who underwent dermatological or neurological evaluation of suspected erythromelalgia at our institution and received a final diagnosis of erythromelalgia were identified from a master diagnosis index covering the period January 1994 to June 2008. A retrospective chart review was performed. Main outcome measures were sensory abnormalities (e.g. pain, burning sensation, tingling) in response to heat, cooling and vibration during computer-assisted sensory testing.

Results. In total, 41 patients with erythromelalgia were enrolled in the study and underwent computer-assisted sensory evaluation. Of these, 34 patients (82.9%) had abnormal results. The commonest abnormality was isolated HPT: 11 patients (26.8%) had heat hypoalgesia and 18 (43.9%) had heat hyperalgesia, whereas only 2 (4.9%) of the healthy control patients had hyperalgesia on testing.

Conclusions. Multiple sensory modalities were found to be abnormal in patients with erythromelalgia, with the commonest clinical abnormality being isolated heat–pain abnormality. These findings lend support to the notion that neuropathy underlies the clinical diagnosis of erythromelalgia. Future studies will explore the nature of the relationship between these sensory abnormalities and the clinical features of erythromelalgia.

Introduction

Erythromelalgia is characterized by warmth, redness and discomfort in parts of the body, such as painful, burning or tingling sensations in the limbs and, most commonly, the feet. The diagnosis is based on these clinical features.

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There is accumulating evidence that erythromelalgia is strongly associated with neuropathy. Both large-fibre and small-fibre neuropathy in patients with erythromelalgia have been reported. Results of electromyographic studies, quantitative sudomotor axon reflex screening,[1,2] and thermoregulatory sweat test (TST)[3] were found to be abnormal in patients with erythromelalgia, and nerve density was decreased in skin biopsies.[3] Orstavik *et al.*[4] suggested that afferent small-fibre dysfunction may help to explain the burning pain commonly associated with erythromelalgia. Indeed, the association with a neuropathy seems to be so strong that we previously raised the question as to whether

erythromelalgia represents a presenting feature of neuropathy.[1] Studies of families with autosomal dominant erythromelalgia have identified mutations in the sodium channel Na(v)1.7, which is expressed selectively within neurones of the nociceptive dorsal root ganglion and sympathetic ganglion.

The inherited form of erythromelalgia has been described as the first inherited painful neuropathy to be understood at a molecular level. In addition, it is regarded as a model disorder that could help elucidate other painful conditions and lead to the development of rational, mechanism-based treatments for pain.[5]

Few studies have examined sensation in erythromelalgia. In our institution, we use quantitative sensation testing with the aid of computers to detect and characterize sensation loss, allodynia and hyperalgesia. This computer-assisted sensory evaluation (CASE) is a standardized quantitative sensation test that was developed by Dyck and colleagues.[6–10] It is composed of several testing measures, including vibratory detection threshold (VDT), cool detection threshold (CDT) and heat–pain threshold (HPT), which evaluate altered sensation for different classes of cutaneous receptors and their nerve fibres. For example, VDT is a measure of the large myelinated A-alpha and B fibres, the small myelinated A-delta fibres, and the small unmyelinated C fibres.

To further characterize the sensory abnormalities associated with erythromelalgia, we carried out quantitative sensation testing in patients with erythromelalgia presenting to our clinic. We used CASE to characterize altered pain (hyperalgesia), vibration and cold detection thresholds in patients with erythromelalgia.

Methods

Participants

The records of patients seen in the departments of dermatology, neurology and vascular medicine at Mayo Clinic (Rochester, MN, USA) during the period January 1994 to June 2008 were identified from a master diagnosis index and reviewed. The inclusion criterion was the diagnosis of erythromelalgia; there were no exclusion criteria.

The patients were referred for dermatological and neurological evaluation of suspected erythromelalgia that affected primarily the distal legs. The diagnosis was based on the clinical features of erythromelalgia: redness and heat in an affected limb. All patients who fulfilled the clinical diagnosis of erythromelalgia had been evaluated previously using tests of vascular and neurological function. A retrospective study was performed on the data related to these test results.

The records of 282 patients were evaluated. Of these, 41 patients (4 men, 37 women; mean ± SD 47 ± 14.25, range 18–76) fulfilled the criteria for the diagnosis of erythromelalgia. Of the 41 patients, 33 were white and 1 was East Asian; the ethnic origin of the remaining 7 patients were unspecified. At the time of presentation, duration of symptoms ranged from 3.6 months to 23 years (mean ± SD 4.5 ± 5.7). The control group consisted of 330 people (165 men, 165 women; mean ± SD 49.7± 15.9, range 18–74) matched for age and gender.

Thermoregulatory sweat test and neurophysiological tests

These tests were performed as previously described.[11] In addition to nerve-conduction studies and needle electromyography to assess large-fibre function, autonomic reflex screening[12,13] was used to evaluate small-fibre function.

Computer-assisted sensory evaluation

CASE is the most sophisticated means of quantitative sensation testing in a predetermined, standardized and controlled testing environment. Patients undergoing CASE must be alert, cooperative and not under the influence of any mind-altering substance at testing.

The system consists of a personal computer, controlling electronics, transducers, a cueing device, a keyboard and ancillary devices, as described by Dyck *et al.*[9] The testing is carried out in a specially equipped laboratory, using standardized techniques. The laboratory is constructed to minimize ambient sensory input (e.g. sight, sound), thus allowing the most accurate data collection. Before testing, standardized instructions are read to all patients. Testing is carried out on defined anatomical sites with preprogrammed stimuli governed by a computer program executing a validated testing algorithm. The tests determine the patient's ability to detect vibration (VDT), cooling (CDT), and heat and pain (HPT). Graded stimuli are applied to a predetermined anatomical site, and patients indicate whether they experience the designated sensation during a specified time.

In this study, the anatomical site chosen was the right or left foot, corresponding to the area where the clinical symptoms of erythromelalgia were most prevalent. CASE was used to obtain VDT, CDT and HPT. HPT

was further divided into three components: the point at which pain is first felt (the HP threshold or HPT 0.5), an intermediate severity of the HP response (HPT 5.0) and the stimulus-response slope [indicates how quickly a subject reaches the intermediate pain level (HPT 5.0) from the baseline (HPT 0.5)].

The data for each sensory test were collected and compared with the cohort of healthy participants who were exposed to identical testing parameters and testing environment. Each patient's results on CASE were grouped by sensory modality, and were considered significant (abnormal) if they were in the 5th percentile (hyperaesthetic) or lower, or in the 95th percentile (hypoesthetic) or higher. These percentiles were derived from a large cohort of healthy people with no underlying neuropathy who had undergone CASE. The size of the percentiles (small or large) represented the magnitude of the stimuli.

To compare the results for different sensory modalities and attributes of nerve conduction, we used percentile values derived from a previous study of healthy people.[10] For each participant who underwent CASE, VDT, CDT and HPT their results were expressed as a specific percentile value that took into account the test site, age, gender and applicable anthropometric characteristics, as described above.

Statistical analysis

The Fisher exact test was used to compare differences in CASE results between patients and controls. An online calculator was used (http://in-silico.net/statistics/fisher_exact_test). $P = 0.05$ was considered significant.

Results

Thermoregulatory sweat test and neurophysiological tests

Of the 41 patients, 21 (51.2%) had an abnormal TST result, 16 (39.0%) had a normal result and 4 (9.8%) had an inconclusive result. Adrenergic function testing identified 10 patients (24.4%) with an abnormal result, 30 (73.2%) with a normal result and 1 (2.4%) with an inconclusive result. For the cardiovagal function testing, 12 patients (29.3%) had an abnormal result, 28 (68.3%) had a normal result and 1 (2.4%) had an inconclusive result.

Computer-assisted sensory examination

The raw-data CASE results were abnormal for 34 of the 41 patients (82.9%) and normal for 7 patients (17.1%) (Fig. 1). The commonest isolated sensory abnormality was HPT detection, which was present in 10 patients (24.4%). Isolated sensory abnormalities were also found for the VDT and CDT tests [five patients (12.2%) each], but to a lesser degree than HPT. Many patients had a combination of sensory abnormalities: both HPT and VDT abnormalities were found in five patients (12.2%); HPT and CDT in five patients (12.2%); VDT and CDT in two patients (4.9%); and HPT, VDT and CDT in two patients (4.9%).

Detailed analysis results by sensory modality

Patients with erythromelalgia had marked hyposensitivity to VDT and CDT compared with controls. Of the

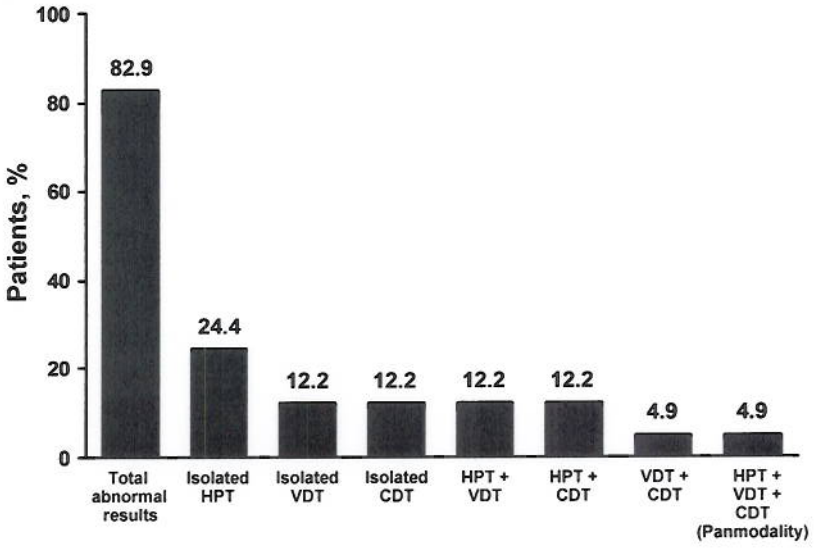

Figure 1 Computer-assisted sensory evaluation abnormalities detected in patients with the diagnosis of erythromelalgia. CDT, cool detection threshold; HPT, heat–pain threshold; VDT, vibratory detection threshold.

41 patients, 11 (26.8%) had hyposensitivity to both VDT and CDT, whereas < 5% of controls had hyposensitivity to either VDT or CDT ($P = 0.001$).

HPT abnormalities were divided into hypoalgesia and hyperalgesia. In the patient group, 11 (26.8%) had hypoalgesia and 18 (43.9%) had hyperalgesia, whereas < 5% of the healthy control patients had either condition ($P = 0.001$).

An additional subcategorization was made for both hypoalgesia and hyperalgesia, dividing them into three groups: group 1 was the baseline HPT, group 2 was the intermediate level of heat–pain sensation, and group 3 was the slope of heat–pain response (velocity). Some patients were in more than one group. Of the 11 patients with hypoalgesia, 5 were in group 1, 7 in group 2 and 8 in group 3. In a comparison with the healthy controls, these results were found to be significant for groups 2 ($P = 0.01$) and 3 ($P < 0.01$) but not group 1 ($P = 0.06$) (Fig. 2a). Of the 18 patients with hyperalgesia, 12 were in group 1, 11 in group 2 and 4 in group 3, and compared with the healthy controls, these results were significant for groups 1 ($P = 0.001$) and 2 ($P = 0.001$) and not group 3 ($P = 0.20$) (Fig. 2b).

Discussion

We obtained data for 41 patients with erythromelalgia who had undergone CASE. Of the 41 patients, 34 (82.9%) had their diagnosis of sensory neuropathy or dysfunction supported by abnormal CASE results. The results confirm that the sensory status of most patients with erythromelalgia is abnormal, which is consistent with previous reports, and corroborate previous data that patients with erythromelalgia have small-fibre neuropathy.

Isolated HPT was the commonest sensory abnormality detected by CASE in our study. Specifically, hyperalgesia was the commonest finding, seen in 18 patients (43.9%). This quantifiable sensory abnormality correlates closely with the clinical findings of erythromelalgia, i.e. the clinical syndrome of warmth, erythema and discomfort in the limbs. The additional findings of CDT and VDT abnormalities suggest the involvement of large and small myelinated fibres in erythromelalgia, which is distinct from the established C-fibre type neuropathy.

Taken together, the results of this study combined with the results of previous neurological studies[1–3,11] provide further evidence that neuropathy is associated with erythromelalgia.

One of the limitations of the study is the possibility of referral bias, as Mayo Clinic is a tertiary centre, receiving the most severely affected patients who have seen many other physicians and may have travelled long distances for evaluation. We acknowledge that the patients in our study may not be representative of the general population of patients with erythromelalgia.

Nevertheless, this study raises numerous questions. There were several types of abnormalities found, but these were not consistent. HPT was the commonest noted abnormality, which was not unexpected, but sometimes presented as hypoalgesia and sometimes as hyperalgesia. It is unclear why this discrepancy exists. Future studies may help to characterize these abnormalities further.

Conclusion

In summary, we found a number of sensory abnormalities among our patients with erythromelalgia.

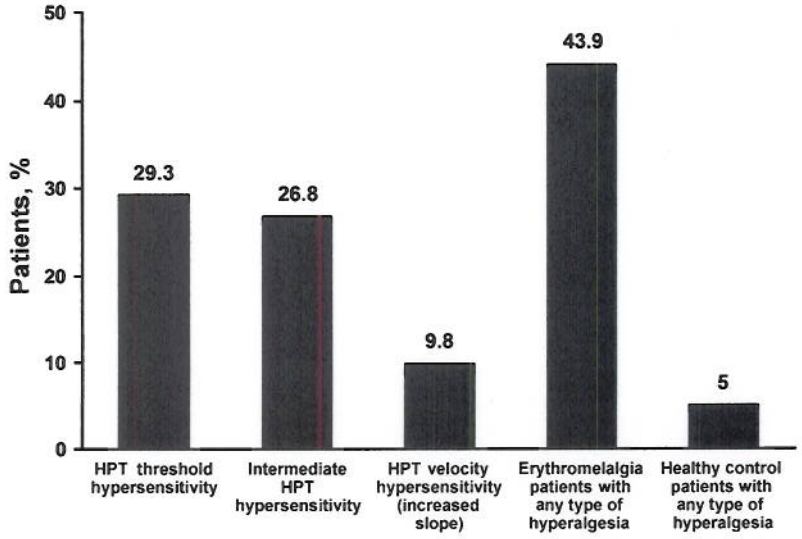

Figure 2 Heat–pain threshold (HPT) in hyperalgesia. The first three bars show the subcategories of HPT, while the last two bars show the overall percentage of HPT abnormalities within the patient and control groups, respectively.

Quantitative sensory testing as measured with CASE was abnormal in 34 of the 41 patients we tested (82.9%). As expected, the commonest abnormality by far was in measurements of HP sensation. To our knowledge, the present study is the first in which extensive sensory testing has been used to characterize sensory neuropathy in patients with erythromelalgia. The strongest advantage of CASE is its capacity to provide quantifiable data for various sensory-conduction abnormalities extending over a range of nerve fibre types. This broader range of analysis allows characterization that has increased our understanding of the sensory abnormalities seen in patients with erythromelalgia.

What is already known about this topic?

- Erythromelalgia is a rare disorder characterized by burning pain, warmth and redness of the limbs.
- The precise pathophysiology of this condition is unknown.
- Microvascular shunting and small-fibre neuropathies have been reported to play a part in symptoms.

What does this study add?

- In this study, multiple sensory modalities were found to be abnormal in patients with erythromelalgia.
- The commonest clinical abnormality was isolated HPT.
- Abnormalities were also found for CDT and VDT.
- Some patients had more than one abnormal reading.

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References

1 Davis MD, Sandroni P, Rooke TW, Low PA. Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia. *Arch Dermatol* 2003; **139**: 1337–43.
2 Sandroni P, Davis MD, Harper CM *et al.* Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. *J Clin Neuromuscul Dis* 1999; **1**: 57–63.
3 Davis MD, Weenig RH, Genebriera J *et al.* Histopathologic findings in primary erythromelalgia are nonspecific: special studies show a decrease in small nerve fiber density. *J Am Acad Dermatol* 2006; **55**: 519–22.
4 Orstavik K, Mork C, Kvernebo K, Jorum E. Pain in primary erythromelalgia: a neuropathic component? *Pain* 2004; **110**: 531–8.
5 Waxman SG, Dib-Hajj S. Erythermalgia: molecular basis for an inherited pain syndrome. *Trends Mol Med* 2005; **11**: 555–62.
6 Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 1997; **49**: 229–39.
7 Dyck PJ, Zimmerman IR, O'Brien PC *et al.* Introduction of automated systems to evaluate touch-pressure, vibration, and thermal cutaneous sensation in man. *Ann Neurol* 1978; **4**: 502–10.
8 Dyck PJ, Litchy WJ, Lehman KA *et al.* Variables influencing neuropathic endpoints: the Rochester Diabetic Neuropathy Study of Healthy Subjects. *Neurology* 1995; **45**: 1115–21.
9 Dyck PJ, O'Brien PC, Johnson DM *et al.* Quantitative sensation testing. In: *Peripheral Neuropathy*, 4th edn (Dyck PJ, Thomas PK, eds). Philadelphia: Elsevier Saunders, 2005; 1063–93.
10 Dyck PJ, O'Brien PC, Davies JL *et al.* Nerve tests expressed as percentiles, normal deviates, and composite scores. In: *Peripheral Neuropathy*, 4th edn (Dyck PJ, Thomas PK, eds). Philadelphia: Elsevier Saunders, 2005; 971–83.
11 Davis MD, Genebriera J, Sandroni P, Fealey RD. Thermoregulatory sweat testing in patients with erythromelalgia. *Arch Dermatol* 2006; **142**: 1583–8.
12 Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc* 1993; **68**: 748–52.
13 Low PA, McLeod JG. Autonomic neuropathies. In: *Clinical Autonomic Disorders: Evaluation and Management*, 2nd edn (Low PA, ed). Philadelphia: Lippincott-Raven Publishers, 1997; 463–86.

